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13. ABSTRACT *(Maximum 200 words)*

To test the hypothesis that estrogen enhances water and sodium retention, we compared the fluid regulatory responses to 150 min of exercise-induced dehydration, followed by 180 min of *ad libitum* drinking during the follicular and luteal phases of the menstrual cycle, and following treatment with an estrogen/progestin oral contraceptive (OCP) and a progestin-only OCP, in a double-blind, randomized, cross-over design. The women (n=9, 25 ± 1 yr, 62.5 ± 3.6 kg,) had a mean blood volume of 67.3 ± 2.1 ml/kg, and a $\dot{V}O_{2peak}$ of 30.6 ± 2.4 $ml \cdot kg^{-1} \cdot min^{-1}$ on the recumbent bicycle ergometer. Due to the double-blind design, the pills have been identified only as OCP-A or B at this point. Preliminary data on 6 women who have completed testing with OCP-A and 5 women with OCP-B reveal a downward shift in osmotic regulation of plasma arginine vasopressin during the luteal phase and both OCP's compared to the follicular phase, which was present during rest and exercise. However, this shift was not accompanied by plasma volume expansion. Fluid and electrolyte loss during exercise were unaffected by phase of the menstrual cycle or OCP treatment. Fluid and electrolyte retention was greatest during *ad libitum* drinking the follicular phase, however, overall fluid balance was similar across all trials.

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Principal Investigator's Signature

10.1.97

Date

TABLE OF CONTENTS

INTRODUCTION

Methods to regulate and suppress menstruation and provide contraception are needed as women take more active roles in the military. The administration of estrogen and progestin combinations in the form of the oral contraceptive pill has been proposed as a method to regulate menstruation in women during combat and field situations. Alternatively, some contraceptive pills provide progestins only, and contain no estrogen. Combined oral contraceptive pills contain synthetic estrogens which exhibit 6-10 times the estrogenic activity provided by endogenous, circulating estrogens. Progestin-only pills not only contain no estrogen, but the unopposed progestin tends to down-regulate estrogen receptors. Thus, these two widely used oral contraceptive preparations differ significantly in their estrogenicity. Estrogens have potent effects on the regulation of body water balance (1, 4), so these two forms of oral contraceptive pills may differ in their effects on water regulation, and hence on physical performance under adverse environmental conditions.

Sex hormone administration is accompanied by significant water and sodium retention (1, 4) which leads to plasma volume expansion (2, 3, 15, 16). In fact, variations in plasma volume at rest and during exercise that are observed following estrogen administration and during different phases of the menstrual cycle are comparable to the reported effects of posture, skin temperature and exercise intensity (9). Bilateral oophorectomy results in a 25% loss of blood volume, and replacement of estrogen restores blood volume (8). Oral contraceptive agents, which deliver pharmacological levels of estrogens, increase total body water (4). Fortney et al. (7) demonstrated an attenuation of the blood volume loss associated with bed rest following estrogen (premarin) administration. Some investigators have shown that plasma volume is higher during the follicular phase, when estrogen levels are rising (12, 13).

The mechanism underlying the estrogen-mediated body water retention is unclear, but may be due to alterations in the release of arginine vasopressin (3, 6). No study has addressed the impact of sex hormone administration on body fluid restoration following dehydration, but arginine vasopressin, measured during controlled rehydration, returns to pre-dehydration levels more slowly in women (follicular phase) compared to men (11). This slower restoration of arginine vasopressin is associated with greater fluid retention in women, suggesting the renal response to arginine vasopressin is unaffected by estrogen. These data suggest a role for estrogen in the recovery of arginine vasopressin following dehydration. No studies have evaluated systematically the impact of variable estrogen doses found in oral contraceptive pills on fluid regulation in women.

Our study was designed to test the hypothesis that oral contraceptive pills containing estrogen increase the thirst and arginine vasopressin response to plasma osmolality and plasma volume alterations during progressive dehydration to a greater degree than progestin-only pills. We expected that this increase in osmotic sensitivity would result in enhanced fluid intake and water retention during a subsequent *ad libitum* rehydration period.

METHODS

Study design:

Ten women volunteered to participate in the dehydration experiments series. Subjects were non smoking, healthy women, ages 21-31, with no contraindications to oral contraceptive use. All subjects were interviewed about their medical history, and had medical and gynecological examinations before admission to the study. During the month preceding the first dehydration/rehydration exposure, blood volume was determined by Evan's Blue dye dilution (procedures are described below). On the same day, following the blood volume assessment, maximal oxygen consumption ($VO_{2peak,}$) was determined with an automated metabolic cart (Sensor Medics Corp, Yorba Linda, CA). The preliminary tests were all conducted in the follicular phase of the menstrual cycle.

Each woman served as her own control. Upon entering the study, the subjects were assigned (double-blind) to undergo experimental testing after four weeks of either continuous combined (estrogen/progestin) or progestin-only treatment. After completing the studies on one treatment protocol, subjects crossed over to the other treatment following a 4 week "washout" period. For estrogen/progestin combined treatment, subjects received 0.35 mg of ethinyl estradiol and 1 mg of the progestin norethindrone daily. For progestin only treatment, subjects receive norethindrone, 1 mg/day. All studies were begun within 2 of the daily pill ingestion when peak serum hormone levels occur (5).

Because sex hormones vary across the menstrual cycle, some variation in the dependent variables over the course of the menstrual cycle may exist, so the study design employed two dehydration baseline studies, carried out in the early-follicular phase (2-5 days after the beginning of menstrual bleeding) and mid-luteal phase of the menstrual cycle. The luteal phase was determined individually by the use of ovulation prediction kits (OvuQuick, Quidel Corp, San Diego, CA) that accurately identify the luteinizing hormone peak. To verify phase of the menstrual cycle, plasma levels of estrogen and progesterone were assessed from the control (pre-exercise) blood sample.

Dehydration experiments

Volunteers arrived at the laboratory between 7:00 - 8:00 am, after having eaten only a prescribed low fat breakfast (~ 300 kcal). The subjects refrained from alcohol and caffeine for 12 h prior to the experiment. Blood volumes were un-manipulated prior to each of the experiments, although subjects were well hydrated by drinking 7 ml/kg body weight of tap water at home before arrival at the laboratory. Upon arriving at the laboratory, the subjects gave a baseline urine sample, were weighed to the nearest 10 g on a beam balance and then sat on the contour chair of a cycle ergometer in the test chamber (27°C, 30% rh) for 60 min of control rest. During the control period, an indwelling catheter was placed in an arm vein. Electrodes and blood pressure cuff were placed and resting blood pressure (Colin Medical Instruments Corp, Komaki, Japan), and heart rate (EKG) recorded at the end of the 60 min control period. At the end of the control period, a (20 ml) blood sample was drawn, control thirst tests (see below) administered and urine collected. Hydration state was assessed from the specific gravity of the control (pre-exercise) urine sample (mean = 1.001).

Following the control period, the chamber temperature was increased to 36°C. The subjects exercised at 50% maximal power output without fluids for 150 min, with 5 min rest periods every 25 min (see "Dehydration protocol" below). Blood samples (10-20 ml) were drawn immediately prior to the rest periods at 60, 120 and 150 min during exercise. Thirst ratings were also assessed immediately prior to rest periods at 30, 60, 90, 120 and 150 min of cycling. During exercise, sealed absorbent patches (Sudormed, Santa Anna, California) were placed on the thigh, forearm, chest, back and forehead for 20-40 min periods for sweat collection. The sweat patch consisted of 4.7 x 3.1 cm filter paper, sealed and affixed to the skin with tegaderm. The area used for the patch was cleaned with deionized water prior to placement and wiped with a clean dry towel. After sampling, the patches were transferred to plastic screw-capped bottles. Local sweat rate was determined by patch weight increase (to 0.0001 g) from the dry weight per min on the skin. The fluid in the patches was collected by centrifugation with nylon MicroFuge centrifuge filter tubes and analyzed for sodium and potassium concentrations. Heart rate and blood pressure were assessed every 10 min throughout exercise. Body weight was determined at 60, 120 and 150 min of exercise, and urine samples were collected at the end of exercise. At the end of exercise, the chamber temperature was reduced to 27° C for the 3.5 h recovery period.

Following dehydration, volunteers rested for 30 min in a contour chair without access to fluids to allow the body fluid compartments to stabilize. Following the stabilization period, subjects drank water *ad libitum* for 180 min. Heart rate and blood pressure were assessed every 10 min throughout stabilization and rehydration. Blood (10 ml) was sampled during the early period of rehydration (just prior to drinking, at 15 min of drinking) and at 30, 60, 120 and 180 min of rehydration (20 ml). Urine samples were collected at each 60 min of rehydration and body weight was measured every 60 min of rehydration.

All blood samples were analyzed for hematocrit, hemoglobin, total protein, osmolality, and the concentrations of creatinine, glucose, urea, sodium, potassium, and arginine vasopressin. The control and final blood samples were analyzed for 17-β-estradiol and progesterone. Blood samples at control, 60, 120 and 150 min of dehydration and at 0, 30, 60, 120 and 180 min of *ad libitum* drinking were also analyzed for the concentration of atrial natriuretic peptide, aldosterone, and plasma renin activity. All urine samples were analyzed for volume, osmolality, and sodium, potassium, and creatinine concentrations.

Dehydration protocol.

We have modified a Monark cycle ergometer by placement of an adjustable contour seat behind the pedals so that the subject was seated with legs nearly in a horizontal position. The exercise intensity was adjusted by changing the tension on the flywheel, and was normalized to each subject by setting the intensity in any given experiment to a pre-determined percentage of maximal aerobic power.

Blood sampling.

All blood sampling was done via a 19 gauge Intracath catheter placed in an arm vein. Subjects were semi-recumbent during placement of the catheter and are seated for 60 min prior to sampling to ensure a steady state in plasma volume and constituents. Blood samples were separated immediately into aliquots. The first was analyzed for hemoglobin and hematocrit. A second aliquot was transferred to a heparinized tube, and third aliquot for the determination of serum sodium and potassium concentrations was placed into a tube without anticoagulant. All other aliquots were placed in tubes containing EDTA. The tubes were centrifuged and the plasma taken off the heparinized sample analyzed for sodium, potassium, osmolality, glucose, urea creatinine and aldosterone. The EDTA samples were analyzed for concentrations of arginine vasopressin and atrial natriuretic peptide and plasma renin activity.

Blood volume

Absolute blood volume was measured by dilution of a known amount of Evan's blue dye. This technique involves injection of an accurately determined volume of dye (by weight, since the specific density is 1.0) into an arm vein and taking blood samples for determination of dilution after complete mixing has occurred (10, 20 and 30 min). Plasma volume was determined from the product of the concentration and volume of dye injected divided by the concentration in plasma after mixing, taking into account 1.5% lost from the circulation within the 10 min. Blood volume was calculated from plasma volume and hematocrit concentration corrected for peripheral sampling.

Thirst ratings

The perception of thirst was assessed by asking the subject to make a mark on a line rating scale in response to the question, 'How thirsty do you feel now?'. The line is 175 mm in length and is marked 'not at all' on one end and 'extremely thirsty' at the 125 mm point. We tell subjects that they can mark beyond the 'extremely thirsty' point if they wish and may even extend the line if they feel it necessary. This method was developed by Marks et al. (10) and has been used with great success in the evaluation of several sensory systems. We have found an extraordinarily good relationship between the perception of thirst and plasma osmolality during hypertonic saline infusion and dehydration in young volunteers.

Calculations

Total water loss due to dehydration was determined from body weight loss. Net fluid gain during rehydration was calculated by subtracting total urine loss from water intake, assuming that respiratory and sweat losses were negligible in the 27°C recovery condition. Electrolyte losses in sweat and urine during dehydration were calculated by multiplying the volume of water loss by the concentration of electrolyte in each fluid. Whole body sweat electrolyte concentration was calculated from sweat rate, local electrolyte concentration and body surface area using the following equation:

$$[E]_m = (0.07[E]_{fh}SR_{fh} + 0.36[E]_{tr}SR_{tr} + 0.13[E]_{fa}SR_{fa} + 0.32[E]_{th}SR_{th}/ 0.07SR_{fh} + 0.36SR_{tr} + 0.13SR_{fa} + 0.32SR_{th}) \quad (14)$$

where the subscripts m, fh, tr, fa and th are whole body mean, forehead, trunk, forearm and thigh; [E] is electrolyte concentration (sodium or potassium, mEq/l), and SR is local sweat rate ($mg \cdot min^{-1} \cdot cm^{-2}$); and the constants 0.07, 0.36, 0.13 and 0.32 represent the percent distribution of body surface in the head, trunk, arms and legs, respectively. Total electrolyte loss from sweat was calculated by multiplying $[E]_m$ and total body sweat loss, calculated from the change in body weight during exercise. Electrolyte losses during rehydration were calculated by multiplying the volume of water loss by the concentration of electrolytes in the urine.

Changes in plasma volume were estimated from changes in hemoglobin (Hb) and hematocrit (hct) concentrations from the control (pre-exercise) sample according to the equation:

$$\% \Delta PV = 100 [[(Hb_b)/(Hb_a)][(1\text{-}hct_a \cdot 10^{-2})]/[(1\text{-}hct_b \cdot 10^{-2})]] - 100$$

where subscripts a and b denote measurements at time a and control, respectively. Hemoglobin is measured in triplicate by the cyanomethemoglobin technique and hematocrit in triplicate by the microhematocrit method.

Fractional excretions of water (FE_{H_2O}) and Na^+ (FE_{Na+}) were calculated from the following equations:

$$FE_{H_2O} = (U_V/GFR) \cdot 100$$

$$FE_{Na+} = (U_V \cdot [Na^+]_u/GFR \cdot [Na^+]_f) \cdot 100$$

$$[Na^+]_f = \text{the Donnan factor for cations } (0.95) \cdot [Na^+]_s$$

where the subscripts f and u are glomerular filtrate and urine respectively, U_v is urine flow rate, and $[Na^+]_s$ is $[Na^+]_s$ in protein-free solution (mEq/kg H_2O). Glomerular filtration rate (GFR) was estimated from creatinine clearance.

Blood analysis:

Plasma, sweat and urine sodium and potassium are measured by flame photometry (Instrumentation Laboratory model 943), plasma osmolality by freezing point depression (Advanced Instruments 3DII), and plasma proteins by refractometry. Plasma glucose, urea and creatinine concentrations are determined by colorimetric assay (Sigma Diagnostic Products). Plasma renin activity, plasma concentrations of aldosterone, atrial natriuretic peptide, arginine vasopressin, 17-β-estradiol and progesterone are measured by radioimmunoassay. Intra-and inter-assay coefficients of variation for the mid-range standard for PRA (4.9 $ng \cdot ml^{-1}$ ANG$\cdot hr^{-1}$) were 2.7% and 6.3% (Incstar Corp), plasma aldosterone (150 pg/ml) were 3.5% and 8.1% (Diagnostic Products), for atrial natriuretic peptide (55.8 pg/ml) were 4.3% and 6.5% (Incstar Corp, Stillwater Minnesota), and for arginine vasopressin (15.3 pg/ml) were 5.3% and 4.8% (Nichols Institute Diagnostics, San Juan Capistrano, CA). Intra-assay coefficients of variation for 17-β-estradiol (47.2 pg/ml) was 3.7% (Diagnostic Products), and for progesterone (3.7 pg/ml) was 2.0% (Diagnostic Products).

RESULTS (preliminary)

In order to maintain the "double-blind" design of these experiments, the two different pills are designated pills "A" and "B," so they will be referred as oral contraceptive pill A (OCP-A) and oral contraceptive pill B (OCP-B) in the sections to follow. As of this date (10/1/97), 6 subjects have completed experiments with OCP-A" and 5 have completed experiments with pill OCP-B Interpretations of the preliminary research is not possible at this point because we do not know which pill contains combined ethinyl estradiol and norethindrone and which is the progestin (norethindrone)- only pill. The data contained in this report only describe *trends*; we have not run statistical analyses because we have complete data on few subjects and hope to avoid premature conclusions and future bias. We expect to complete all data collection by the end of December 1997 or early January 1998.

Of the 10 volunteers, one subject dropped out after her first two baseline tests for personal reasons, so all of her data have been excluded. Another woman had to stop OCP-A because of severe nausea. She had completed all 4 control dehydration tests, and the dehydration test on OCP-B. All of her control data for OCP-A have been excluded. Therefore, the final analysis will compare the dehydration test responses of 9 women on OCP-B with their two control tests, 8 women on OCP-A with their control tests, and will compare the responses of 8 women between OCP-A and OCP-B. Please note that the results presented for this progress report for OCP-A and OCP-B are not from the same subjects: the subjects were randomly assigned to receive OCP-A or OCP-B first, so only 4 subjects have completed all six experimental days.

The women (n=9) have a mean age 25 ± 1 yr, mean body weight of 62.5 ± 3.6 kg, and a mean height of 164 ± 3 cm. The women are all physically active, with a mean blood volume of 67.3 ± 2.1 ml/kg, and a VO_{2peak} of 30.6 ± 2.4 $ml \cdot kg^{-1} \cdot min^{-1}$ on the recumbent bicycle ergometer.

Analysis of plasma concentrations of 17-beta estradiol $[E_2]_p$ and progesterone $[P_4]_p$ indicated that all subjects met the criteria for the follicular and mid-luteal phases of the menstrual cycle (Table 1). Data for plasma concentrations of sex hormones were not provided to the investigators in order to maintain the integrity of the double-blind experimental design.

Oral contraceptive Pill A

Control

Body weight before exercise in the luteal phase (62.9 ± 4.5) was lower relative to the follicular phase (65.1 ± 4.7 kg) and OCP-A (64.6 ± 4.5 kg). Pre-exercise heart rate and blood pressure were similar during the follicular and luteal phases and unaffected by OCP-A administration (Table 2A). Urine flow, free water and osmolar clearances were similar within subjects prior to each exercise test (Table 3A). However, pre-exercise urine osmolality, and urine:plasma osmolality were reduced during the luteal phase (Table 3A). Baseline thirst measurements were low, and unaffected by menstrual phase or OCP administration (Fig. 2).

Blood components.

Plasma osmolality was reduced in both the luteal phase and following one month of oral contraceptive OCP-A relative to the follicular phase (Fig. 1). Table 4A shows very little change with other blood components over the course of the menstrual cycle, or in response to either OCP-A, although plasma concentration of sodium was somewhat lower during the luteal phase and following administration of OCP-A. Baseline levels of plasma glucose and urea were unaffected by menstrual phase or OCP-A administration, indicating that the fall in plasma osmolality was due to the fall in plasma sodium levels.

Pre-exercise plasma concentration of arginine vasopressin was unaffected by phase of the menstrual cycle (Fig. 3, 1.5 ± 0.3 and 1.3 ± 0.0 pg/ml, for follicular and luteal phases, respectively), however arginine vasopressin tended to increase with OCP-A administration (2.2 ± 0.9 pg/ml). Plasma renin activity (PRA) was increased during the luteal phase of the menstrual cycle compared to the follicular phase and to OCP-A administration (Table 5A). The same was true for plasma aldosterone concentrations (Table 5A). In addition, PRA and plasma aldosterone concentration were slightly higher following OCP-A relative to pre-exercise concentrations of these hormones during the follicular phase. Plasma concentration of atrial natriuretic peptide was unaffected by menstrual phase, or by OCP-A administration.

Exercise responses.

Body water and electrolyte loss.

At the end of 150 min of exercise at 36°C, the women lost 1.5 ± 0.2, 1.4 ± 0.1 and 1.5 ± 0.1 kg through sweating during the follicular and luteal phases and OCP-A, respectively. Urine flow, free water clearance and fractional water excretion were reduced, and the excretion of sodium and potassium were increased by exercise to a similar extent in all three conditions (Table 3A).

Sodium losses from sweat were lowest during exercise in the luteal phase (46.7 ± 11.1 mEq), but there were no differences in sweat sodium loss between the follicular phase (55.1 ± 8.5 mEq) and during OCP-A administration (53.9 ± 12.7 mEq). Sweat potassium losses were similar during all three exercise tests (5.91 ±0.63, 5.75 ± 0.27 and

5.97 ± 0.76 mEq, for follicular and luteal phases, and OCP-A, respectively). Thirst ratings were unaffected by menstrual phase or OCP-A administration (Fig. 2).

Cardiovascular variables.

Heart rate and blood pressure responses to exercise were similar during the follicular and luteal phases, but heart rate was 10 beats/min lower with OCP-A administration at the end of exercise (Table 2A). Systolic and pulse blood pressures increased, and diastolic blood pressure decreased similarly during exercise regardless of menstrual phase or administration of OCP-A.

Blood components.

Exercise increased plasma osmolality, and the concentrations of plasma electrolytes similarly during the follicular and luteal phases, and during OCP-A administration (see Fig. 1, Table 2A). In addition, hematocrit and hemoglobin responses were also increased to a similar extent, so calculated percent change in plasma volume (%Δ PV) at the end of exercise was similar in the follicular (-10.1 ± 1.2 %) and luteal (-9.3 ± 2.3 %) phases, and following administration of OCP-A (-9.2 ± 1.4 %).

Plasma concentrations of arginine vasopressin were increased during exercise, but appeared to have the greatest increase during exercise in the luteal phase, increasing by 3.0 ± 1.4 pg/ml, compared to 2.2 ± 0.6, and 2.1 ± 0.7 pg/ml, for follicular and luteal phases and OCP-A respectively (Fig. 3). Plasma renin activity in the luteal phase remained elevated through exercise relative to levels during the follicular phase and OCP-A (Table 5A), as did the plasma concentration of aldosterone. Plasma concentration of atrial natriuretic peptide increased during exercise, but was unaffected by menstrual phase, or by OCP-A administration.

Ad libitum rehydration

At 180 min of *ad libitum* rehydration, pre-exercise body weight was only partially restored to 64.2 ± 4.7, 62.1 ± 4.5 and 63.7 ± 4.4 kg which represented a 1.4 %, 1.0 % and 1.1 % body water restoration during the follicular phase, the luteal phase, and OCP-A administration, respectively. Heart rate and blood pressure recovered at similar rates across the three treatments (Table 2A). Thirst ratings during rehydration were also unaffected by menstrual phase or OCP-A administration (Fig. 2). Fluid intake was higher during the follicular phase compared to OCP-A, but there were no differences between the luteal phase and OCP-A administration (Fig. 4).

Blood components.

Plasma osmolality in the follicular phase remained elevated throughout the rehydration period compared to the luteal phase and OCP-A administration (Fig. 1). Table 4A shows very little change in other blood components over the course of the menstrual cycle, or in response to either OCP-A, although plasma concentration of sodium was somewhat higher during the follicular phase and following administration of OCP-A, reflecting the lower plasma osmolality. Plasma glucose and urea concentrations were

unaffected by menstrual phase or OCP-A administration, indicating that the changes in plasma osmolality were due to the changes in the concentration of plasma sodium levels.

Recovery of plasma arginine vasopressin levels occurred rapidly following the beginning of *ad libitum* drinking during both phases of the menstrual cycle and OCP-A administration (Fig. 3), but appeared still elevated in the latter 120 min of rehydration during OCP-A compared to the luteal phase. Despite the resting and exercise augmentation of PRA during the luteal phase of the menstrual cycle, PRA levels were similar for all three conditions (Table 5A). However, plasma aldosterone concentration followed the earlier pattern, and remained elevated in the luteal phase throughout the rehydration period (Table 5A), although aldosterone concentration was similar between the follicular phase and OCP-A administration. Again, plasma concentration of atrial natriuretic peptide was unaffected by menstrual phase, or by OCP-A administration during rehydration.

Renal water and electrolyte regulation.

Urine flow, renal free water clearance and fractional water excretion were greater during rehydration in the follicular phase compared to the luteal phase or during OCP-A. However, overall fluid balance was unaffected by phase of the menstrual cycle or administration of OCP-A (Fig. 4). Renal electrolyte excretion was not affected either by phase of the menstrual cycle, or by administration of OCP-A (Table 3A).

Oral contraceptive Pill B

Control

Body weight before exercise was unaffected by menstrual phase or administration of OCP-B (61.9 ± 4.6, 60.8 ± 4.3 and 61.0 ± 4.4, for the follicular phase, the luteal phase and OCP-B, respectively). Further, pre-exercise heart rate and blood pressure were similar during the follicular and luteal phases and unaffected by OCP-B administration (Table 2B). Urine flow, free water clearance, and fractional excretion of free water were greater in the follicular phase relative to the two other experimental days (Table 3B). However, pre-exercise urine osmolality was similar among the three days, while urine:plasma osmolality was increased during the luteal phase (Table 3B).

Blood components.

Plasma osmolality was reduced in both the luteal phase and following one month of oral contraceptive OCP-B administration relative to the follicular phase (Fig. 1). Table 4B shows very little change in other blood components over the course of the menstrual cycle, or in response to OCP-B, except in plasma concentration of sodium, which was lower during the luteal phase and following administration of OCP-B. Baseline levels of plasma glucose and urea were unaffected by menstrual phase or OCP-B administration, indicating that the fall in plasma osmolality was due to the fall in plasma sodium levels.

Pre-exercise plasma concentration of arginine vasopressin was unaffected by phase of the menstrual cycle (Fig. 3, 1.7 ± 0.6 and 2.0 ± 0.4 pg/ml, for follicular and luteal

phases, respectively), or by administration of OCP-B administration (2.3 ± 0.3 pg/ml). Plasma renin activity was reduced during the follicular phase, compared to the luteal phase and to OCP-B administration (Table 5B). The response was similar for plasma aldosterone concentrations (Table 3B). In addition, PRA was slightly higher following OCP-B relative to the follicular phase. Plasma concentration of atrial natriuretic peptide was unaffected by menstrual phase, or by OCP-B administration.

Exercise responses.

Body water and electrolyte loss.

At the end of 150 min of exercise at 36°C, the women lost 1.5 ± 0.1, 1.4 ± 0.1 and 1.3 ± 0.1 kg through sweating during the follicular and luteal phases and OCP-B, respectively. Urine flow, free water clearance and fractional water excretion were reduced to a similar extent in all three conditions (Table 3B). The excretion of sodium in urine was increased by exercise in all three conditions, but this increase was somewhat attenuated in the luteal phase. Potassium excretion was also increased by exercise in all three conditions, with the greatest increase during OCP-B administration.

Sodium losses from sweat were greatest during exercise in the follicular phase (66.6 ± 5.7 mEq), compared to exercise in the luteal phase (57.2 ± 9.3 mEq) and OCP-B administration (68.5 ± 10.5 mEq). Sweat potassium losses were similar during all three exercise tests (5.97 ±0.76, 5.96 ± 0.80 and 5.10 ± 0.54 mEq, for the follicular phase, luteal phase and OCP-B administration, respectively). Thirst ratings increased during exercise, but the increase was unaffected by menstrual phase or OCP-B administration (Fig. 2).

Cardiovascular variables.

Heart rate and blood pressure responses to exercise were similar during the follicular and luteal phases, and during OCP-B (Table 4B). Systolic and pulse blood pressures increased, and diastolic blood pressure decreased similarly during exercise regardless of menstrual phase or administration of OCP-A.

Blood components.

Exercise increased plasma osmolality, and the concentrations of plasma electrolytes similarly during the follicular and luteal phases, and during OCP-B administration (see Fig. 1, Table 3B). In addition, hematocrit and hemoglobin responses were also increased to a similar extent, so calculated %Δ PV at the end of exercise was similar in the follicular (-9.1 ± 0.9 %) and luteal (-8.8 ± 1.0 % phases, and following administration of OCP-B (-8.5 ± 0.7 %).

Plasma concentrations of arginine vasopressin were increased during exercise under all three conditions, but the increase appeared attenuated during exercise in the follicular phase (Fig. 3). Plasma renin activity in the luteal phase remained elevated through exercise relative to levels during the follicular phase and OCP-B (Table 3B), as did the plasma concentration of aldosterone. Plasma concentration of atrial natriuretic peptide increased during exercise, but was unaffected by menstrual phase, or by OCP-B administration.

Ad libitum rehydration

At 180 min of *ad libitum* rehydration, pre-exercise body weight was only partially restored to 60.7 ± 4.5, 60.2 ± 4.3, 60.0 ± 4.4 kg which represented a 2.0 %, 1.2 % and 1.4 % body water restoration during the follicular phase, the luteal phase, and OCP-B administration, respectively. Heart rate recovered most rapidly in the follicular phase, but blood pressure recovered at a similar rate across the three treatments (Table 2B). Thirst ratings during rehydration were also unaffected by menstrual phase or OCP-B administration (Fig, 2). Fluid intake was unaffected by menstrual phase or OCP-B administration (Fig. 4).

Blood components.

Plasma osmolality in the follicular phase remained elevated throughout the rehydration period compared to rehydration during the luteal phase and OCP-B administration (Fig. 1). Table 4B shows very little change with other blood components over the course of the menstrual cycle, or in response to either OCP-B, although plasma concentration of sodium was greater during the follicular phase, reflecting the greater plasma osmolality. During rehydration, plasma glucose and urea concentrations were unaffected by menstrual phase or OCP-B administration, indicating that the lower plasma osmolality was due to the lower plasma sodium concentration.

Recovery of plasma arginine vasopressin levels occurred rapidly following the beginning of *ad libitum* drinking during both phases of the menstrual cycle and OCP-B administration (Fig. 3), and remained low throughout rehydration except for some fluctuation during OCP-B administration. Plasma renin activity was lower during the follicular phase of the menstrual cycle relative to the luteal phase and OCP-B (Table 5B), which was also true for plasma aldosterone concentration throughout the rehydration period (Table 5B). Again, plasma concentration of atrial natriuretic peptide was unaffected by menstrual phase, or by OCP-B administration during rehydration.

Renal water and electrolyte regulation.

Urine flow, renal free water clearance and fractional water excretion appeared unaffected by phase of the menstrual cycle or by administration of OCP-B (Table 5B). Overall fluid balance was unaffected by phase of the menstrual cycle or administration of OCP-B (Fig. 4). Renal sodium excretion was lower during the luteal phase relative to the follicular phase and OCP-B, but there was very little difference in potassium excretion between the three tests (Table 3B).

CONCLUSIONS

We have avoided conclusions based on these data to avoid future bias. Interpretations and conclusions will follow completion of all data collection.

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Text to Figures.

Figure 1. Plasma osmolality ($Osm_{p,}$) response to dehydrating exercise and 180 min of *ad libitum* rehydration in the follicular and luteal phases, and during administration of oral contraceptive pills A (OCP-A n = 6, *top*) and B (OCP-B n=5, *bottom*). Data are expressed as mean ± SEM.

Figure 2. Perceptions of thirst in response to dehydrating exercise and 180 min of *ad libitum* rehydration in the follicular and luteal phases, and during administration of oral contraceptive pills A (OCP-A n = 6, *top*) and B (OCP-B n=5, *bottom*). Data are expressed as mean ± SEM.

Figure 3. Plasma arginine vasopressin concentration ($[AVP]_p$) response to dehydrating exercise and 180 min of *ad libitum* rehydration in the follicular and luteal phases, and during administration of oral contraceptive pills A (OCP-A n = 4, *top*) and B (OCP-B n=4, *bottom*). Data are expressed as mean ± SEM.

Figure 4. Cumulative fluid intake and urine output during dehydrating exercise and 180 min of *ad libitum* rehydration in the follicular and luteal phases, and during administration of oral contraceptive pills A (OCP-A n = 6, *top left*) and B (OCP-B n=5, *top right*). Bottom graphs demonstrate net fluid gain during *ad libitum* rehydration for OCP-A (*left*) and OCP-B (*right*). Data are expressed as mean ± SEM.

Hormone	Follicular A	Luteal A	OCP-A	Follicular B	Luteal B	OCP-B
17-β estradiol	27.3 ± 5.6	105.1 ± 26.2	---	26.1 ± 6.7	146.7 ± 38.3	---
Progesterone	1.32 ± 0.62	10.7 ± 3.1	---	0.49 ± 1.0	13.62 ± 2.1	---

Table 1. Pre-exercise plasma concentrations of endogenous 17-β estradiol and progesterone in the follicular and luteal phases and during oral contraceptive administration with pill A (OCP-A, n=6) and pill B (OCP-B, n=5). Data for plasma concentrations of sex hormones were not provided to the investigators in order to maintain the integrity of the double-blind experimental design. Data are expressed as mean ± SEM.

	Pre-Exercise	End-exercise	Rehydration		
	0 min	150 min	0 min	120 min	180 min
HR, beats/min					
Follicular	75 ± 5	152 ± 4	90 ± 6	77 ± 5	77 ± 5
Luteal	76 ± 7	152 ± 2	92 ± 5	80 ± 7	79 ± 8
OCP-A	79 ± 4	141 ± 6	89 ± 7	79 ± 5	77 ± 5
MAP, mm Hg					
Follicular	85 ± 2	83 ± 5	78 ± 2	81 ± 3	78 ± 1
Luteal	82 ± 2	81 ± 4	78 ± 2	76 ± 2	77 ± 2
OCP-A	83 ± 1	82 ± 5	78 ± 2	77 ± 3	78 ± 2
SBP, mm Hg					
Follicular	115 ± 2	142 ± 10	112 ± 2	104 ± 3	108 ± 3
Luteal	115 ± 4	138 ± 9	115 ± 5	105 ± 2	107 ± 3
OCP-A	120 ± 2	141 ± 9	112 ± 1	109 ± 2	111 ± 1
DBP, mm Hg					
Follicular	70 ± 2	53 ± 2	61 ± 2	69 ± 6	63 ± 1
Luteal	65 ± 3	52 ± 4	59 ± 1	62 ± 3	62 ± 3
OCP-A	65 ± 1	53 ± 4	61 ± 3	61 ± 4	62 ± 3
PP, mm Hg					
Follicular	46 ± 2	88 ± 8	52 ± 2	35 ± 8	45 ± 3
Luteal	50 ± 7	86 ± 9	56 ± 4	43 ± 5	45 ± 5
OCP-A	54 ± 3	88 ± 7	51 ± 3	49 ± 3	49 ± 3

Table 2A. Heart rate (HR), mean (MAP), systolic (SBP), diastolic (DBP) and pulse (PP) blood pressures at rest and in response to 150 min dehydrating exercise and 180 of *ad libitum* rehydration in the follicular and luteal phases, and during administration of oral contraceptive pill A (OCP-A, n=6). Data are expressed as mean ± SEM.

	Pre-Exercise	End-exercise	Rehydration		
	0 min	150 min	0 min	120 min	180 min
HR, beats/min					
Follicular	81 ± 4	149 ± 4	89 ± 6	74 ± 1	77 ± 2
Luteal	84 ± 5	150 ± 2	99 ± 3	82 ± 4	88 ± 4
OCP-B	83 ± 4	156 ± 9	97 ± 6	88 ± 5	86 ± 3
MAP, mm Hg					
Follicular	88 ± 3	82 ± 7	83 ± 7	77 ± 2	79 ± 3
Luteal	82 ± 2	85 ± 3	73 ± 2	79 ± 2	78 ± 2
OCP-B	82 ± 2	82 ± 2	76 ± 3	83 ± 2	79 ± 3
SBP, mm Hg					
Follicular	119 ± 4	140 ± 10	112 ± 6	105 ± 3	109 ± 3
Luteal	112 ± 3	134 ± 7	102 ± 3	108 ± 3	105 ± 2
OCP-B	115 ± 5	136 ± 4	109 ± 3	112 ± 3	110 ± 3
DBP, mm Hg					
Follicular	72 ± 2	53 ± 7	68 ± 2	63 ± 6	64 ± 1
Luteal	67 ± 3	61 ± 4	59 ± 2	65 ± 3	65 ± 3
OCP-B	66 ± 3	56 ± 4	59 ± 4	69 ± 1	63 ± 4
PP, mm Hg					
Follicular	46 ± 2	87 ± 8	44 ± 6	42 ± 4	45 ± 3
Luteal	44 ± 3	73 ± 7	43 ± 3	43 ± 3	40 ± 5
OCP-B	49 ± 6	80 ± 8	49 ± 5	43 ± 3	46 ± 3

Table 2B. Heart rate (HR), mean (MAP), systolic (SBP), diastolic (DBP) and pulse (PP) blood pressures at rest and in response to 150 min dehydrating exercise and 180 of *ad libitum* rehydration in the follicular and luteal phases, and during administration of oral contraceptive pill B (OCP-B, n=5). Data are expressed as mean ± SEM.

	Pre-Exercise	End-exercise	Rehydration		
Pre	0 min	150 min	60 min	120 min	180 min
GFR, ml/min					
Follicular	113.0 ± 12.3	81.9 ± 12.3	79.1 ± 13.6	102.4 ± 13.8	92.3 ± 10.2
Luteal	120.4 ± 7.7	83.9 ± 13.9	64.5 ± 10.3	80.2 ± 12.9	98.7 ± 16.0
OCP-A	115.0 ± 6.7	86.1 ± 14.3	75.2 ± 13.1	83.7 ± 12.8	88.0 ± 13.1
U_v, ml/min					
Follicular	4.2 ± 1.5	1.0 ± 0.3	0.7 ± 0.2	2.1 ± 0.8	3.0 ± 1.0
Luteal	4.3 ± 1.3	1.2 ± 0.3	0.5 ± 0.1	0.7 ± 0.2	1.4 ± 0.5
OCP-A	3.7 ± 0.9	0.9 ± 0.2	0.5 ± 0.1	0.5 ± 0.2	0.8 ± 0.4
Osm_u, mosmol/kg H_2O					
Follicular	300 ± 173	500 ± 96	822 ± 119	590 ± 156	426 ± 181
Luteal	179 ± 61	403 ± 92	914 ± 36	722 ± 107	520 ± 149
OCP-A	273 ± 127	507 ± 103	927 ± 50	842 ± 97	772 ± 138
Osm_u/Osm_p					
Follicular	1.2 ± 0.6	1.9 ± 0.4	3.0 ± 0.5	2.4 ± 0.6	1.7 ± 0.8
Luteal	0.4 ± 0.1	1.2 ± 0.3	2.7 ± 0.7	2.9 ± 0.3	2.1 ± 0.6
OCP-A	1.1 ± 0.5	1.7 ± 0.5	3.3 ± 0.2	2.3 ± 0.7	2.7 ± 0.6
C_{H_2O}, ml/min					
Follicular	2.3 ± 1.4	-0.4 ± 0.2	-0.9 ± 0.2	-0.5 ± 0.3	1.2 ± 0.8
Luteal	2.6 ± 1.1	-0.1 ± 0.3	-1.0 ± 0.1	-0.8 ± 0.1	0.1 ± 0.4
OCP-A	1.8 ± 0.9	0.5 ± 0.2	-1.0 ± 0.1	-1.0 ± 0.1	-0.6 ± 0.3
C_{osm}, ml/min					
Follicular	1.9 ± 0.2	1.4 ± 0.9	1.6 ± 0.1	1.9 ± 0.2	1.9 ± 0.2
Luteal	1.7 ± 0.2	1.2 ± 0.2	1.4 ± 0.1	1.5 ± 0.1	1.5 ± 0.1
OCP-A	1.8 ± 0.1	1.4 ± 0.1	1.5 ± 0.1	1.6 ± 0.2	1.4 ± 0.2
FE_{Na+}, %					
Follicular	0.52 ± 0.12	0.50 ± 0.16	0.87 ± 0.17	0.57 ± 0.06	0.51 ± 0.06
Luteal	0.29 ± 0.07	0.36 ± 0.10	0.68 ± 0.18	0.50 ± 0.10	0.47 ± 0.13
OCP-A	0.41 ± 0.08	0.47 ± 0.15	0.70 ± 0.10	0.76 ± 0.13	1.02 ± 0.38
FE_{H_2O}, %					
Follicular	3.65 ± 1.27	1.16 ± 0.26	0.85 ± 0.14	1.24 ± 0.31	3.06 ± 0.88
Luteal	3.39 ± 0.94	1.50 ± 0.25	0.85 ± 0.20	0.82 ± 0.15	1.23 ± 0.23
OCP-A	3.27 ± 0.82	1.11 ± 0.22	0.67 ± 0.09	0.74 ± 0.11	0.93 ± 0.24
U_{Na+}, mEq					
Follicular	5.5 ± 1.2	9.4 ± 2.7	9.2 ± 1.1	6.3 ± 1.1	3.8 ± 0.4
Luteal	3.1 ± 0.8	6.6 ± 2.3	5.6 ± 1.4	4.6 ± 1.4	3.3 ± 0.6
OCP-A	4.1 ± 0.6	7.8 ± 2.2	6.5 ± 0.9	5.8 ± 2.3	9.1 ± 4.8
U_{K+}, mEq					
Follicular	2.3 ± 0.5	8.6 ± 2.3	7.5 ± 1.9	5.8 ± 1.9	3.3 ± 0.5
Luteal	4.3 ± 2.5	9.4 ± 1.9	5.0 ± 2.2	3.2 ± 1.2	2.4 ± 0.4
OCP-A	2.0 ± 0.6	8.8 ± 2.0	5.2 ± 1.4	4.2 ± 1.4	4.2 ± 1.2
$[Na^+]_u/[K^+]_u$					
Follicular	2.4 ± 0.2	1.1 ± 0.2	1.6 ± 0.3	1.5 ± 0.3	1.4 ± 0.3
Luteal	2.1 ± 0.8	0.8 ± 0.2	2.8 ± 1.3	6.5 ± 4.9	1.7 ± 0.5
OCP-A	3.0 ± 0.8	1.0 ± 0.3	1.6 ± 0.3	1.4 ± 0.3	2.7 ± 1.0

	Pre-Exercise	End-exercise	Rehydration		
Pre	0 min	150 min	60 min	120 min	180 min
GFR, ml/min					
Follicular	123.4 ± 14.3	100.3 ± 13.1	94.8 ± 11.7	88.3 ± 20.3	87.7 ± 19.6
Luteal	129.7 ± 7.6	90.0 ± 13.2	88.1 ± 16.5	99.6 ± 19.7	99.3 ± 15.3.
OCP-B	134.2 ± 8.1	90.3 ± 12.3	82.2 ± 6.4	80.0 ± 8.3	84.2 ± 11.8
U_v, ml/min					
Follicular	7.0 ± 1.1	1.6 ± 0.5	0.6 ± 0.1	1.0 ± 0.4	0.9 ± 0.3
Luteal	4.9 ± 1.3	1.1 ± 0.2	0.5 ± 0.0	0.5 ± 0.1	0.6 ± 0.1
OCP-B	5.4 ± 0.7	1.2 ± 0.2	0.5 ± 0.1	0.8 ± 0.3	0.9 ± 0.4
Osm_u, mosmol/kg H_2O					
Follicular	99 ± 12	322 ± 49	927 ± 88	798 ± 146	692 ± 131
Luteal	177 ± 59	465 ± 111	931 ± 44	908 ± 49	825 ± 97
OCP-B	117 ± 28	384 ± 58	832 ± 42	685 ± 141	515 ± 158
Osm_u/Osm_p					
Follicular	0.4 ± 0.0	1.3 ± 0.2	3.1 ± 0.3	2.7 ± 0.4	2.1 ± 0.5
Luteal	0.6 ± 0.2	1.7 ± 0.5	3.3 ± 0.1	3.2 ± 0.2	3.0 ± 0.3
OCP-B	0.4 ± 0.1	1.2 ± 0.2	3.0 ± 0.1	2.4 ± 0.5	1.8 ± 0.6
C_{H_2O}, ml/min					
Follicular	4.7 ± 0.9	0.0 ± 0.3	-1.1 ± 0.2	-1.0 ± 0.4	-0.8 ± 0.2
Luteal	2.6 ± 1.3	-0.4 ± 0.3	-1.0 ± 0.2	-1.0 ± 0.1	-1.0 ± 0.1
OCP-B	3.4 ± 0.9	-0.4 ± 0.3	-1.0 ± 0.1	-0.6 ± 0.4	-0.3 ± 0.4
C_{osm}, ml/min					
Follicular	2.3 ± 0.3	1.6 ± 0.4	1.6 ± 0.3	1.9 ± 0.3	1.7 ± 0.2
Luteal	1.9 ± 0.3	1.4 ± 0.1	1.5 ± 0.2	1.5 ± 0.2	1.5 ± 0.1
OCP-B	2.0 ± 0.2	1.6 ± 0.4	1.5 ± 0.1	1.5 ± 0.1	1.2 ± 0.3
FE_{Na+}, %					
Follicular	0.5 ± 0.1	0.5 ± 0.2	1.2 ± 0.4	1.0 ± 0.4	1.0 ± 0.3
Luteal	0.4 ± 0.7	0.6 ± 0.4	1.2 ± 1.0	0.5 ± 0.2	0.3 ± 0.1
OCP-B	0.4 ± 0.1	0.5 ± 0.2	0.7 ± 0.1	0.6 ± 0.1	0.6 ± 0.2
FE_{H_2O}, %					
Follicular	6.3 ± 1.1	1.4 ± 0.3	1.1 ± 0.2	1.4 ± 0.4	1.7 ± 0.6
Luteal	4.2 ± 1.3	1.4 ± 0.3	1.1 ± 0.5	0.7 ± 0.2	0.6 ± 0.1
OCP-B	4.0 ± 0.5	1.4 ± 0.2	0.7 ± 0.1	1.2 ± 0.5	1.4 ± 0.7
U_{Na+}, mEq					
Follicular	6.11 ± 1.2	11.8 ± 4.4	10.1 ± 2.4	5.9 ± 2.0	6.0 ± 1.7
Luteal	4.7 ± 0.9	6.4 ± 2.0	4.7 ± 1.3	2.9 ± 0.6	3.1 ± 0.5
OCP-B	4.9 ± 0.9	12.5 ± 4.1	11.2 ± 3.2	9.3 ± 4.5	9.2 ± 5.6
U_{K+}, mEq					
Follicular	2.3 ± 0.9	6.8 ± 1.5	4.9 ± 1.4	2.6 ± 0.7	2.4 ± 0.4
Luteal	3.5 ± 1.0	8.8 ± 1.2	6.0 ± 1.0	3.4 ± 0.3	3.7 ± 0.7
OCP-B	2.7 ± 1.2	11.4 ± 5.8	5.2 ± 2.0	2.8 ± 0.7	1.8 ± 0.7
$[Na^+]_u/[K^+]_u$					
Follicular	3.7 ± 1.1	1.9 ± 0.6	3.4 ± 1.3	2.7 ± 0.7	2.4 ± 0.5
Luteal	2.0 ± 0.9	0.8 ± 0.3	1.1 ± 0.5	0.9 ± 0.2	0.9 ± 0.2
OCP-B	2.7 ± 1.0	1.1 ± 0.5	2.3 ± 0.8	2.0 ± 0.7	2.2 ± 0.8

Text to Tables 3A and 3B

Table 3A. Renal function and fluid regulatory responses to dehydrating exercise and 180 min of *ad libitum* rehydration in the follicular and luteal phases, and during administration of oral contraceptive pill A (OCP-A, n=6). Glomerular filtration rate (GFR), urine osmolality (Osm_u), free water clearance (C_{H_2O}), osmolar clearance (C_{osm}), fractional excretions of sodium (FE_{Na+}) and water (FE_{H_2O}), urine excretion of sodium (U_{Na+}) and potassium (U_{K+}), and ratio of urine sodium and potassium concentrations ($[Na^+]_u/[K^+]_u$). Data are mean ± SEM.

Table 3B. Renal function and fluid regulatory responses to dehydrating exercise and 180 min of *ad libitum* rehydration in the follicular and luteal phases, and during administration of oral contraceptive pill B (OCP-B, n=5). Glomerular filtration rate (GFR), urine osmolality (Osm_u), free water clearance (C_{H_2O}), osmolar clearance (C_{osm}), fractional excretions of sodium (FE_{Na+}) and water (FE_{H_2O}), urine excretion of sodium (U_{Na+}) and potassium (U_{K+}), and ratio of urine sodium and potassium concentrations ($[Na^+]_u/[K^+]_u$). Data are mean ± SEM.

	Pre-exercise	Exercise			Rehydration			
	0 min	60 min	120 min	150 min	0 min	60 min	120 min	180 min
Hct , %								
Follicular	35.6 ± 0.9	37.2 ± 0.9	37.8 ± 1.0	37.7 ± 1.1	36.1 ± 0.8	35.7 ± 0.8	36.0 ± 1.0	35.7 ± 1.0
Luteal	36.4 ± 1.2	37.9 ± 1.1	38.0 ± 1.2	39.3 ± 1.1	36.8 ± 1.2	36.6 ± 1.1	36.5 ± 1.2	36.5 ± 1.4
OCP-A	35.3 ± 0.6	36.6 ± 0.6	36.8 ± 0.6	37.1 ± 0.8	35.2 ± 0.6	35.1 ± 0.6	34.7 ± 0.7	34.7 ± 0.6
Hb, g/dl								
Follicular	12.2 ± 0.3	12.9 ± 0.3	13.1 ± 0.3	13.1 ± 0.4	12.7 ± 0.4	12.2 ± 0.3	12.2 ± 0.3	12.1 ± 0.4
Luteal	12.4 ± 0.5	13.0 ± 0.5	13.1 ± 0.5	13.4 ± 0.4	12.7 ± 0.4	12.4 ± 0.5	12.4 ± 0.5	12.3 ± 0.6
OCP-A	11.8 ± 0.3	12.5 ± 0.3	12.6 ± 0.3	12.7 ± 0.4	12.0 ± 0.3	11.8 ± 0.3	11.9 ± 0.3	11.9 ± 0.3
$[Na^+]_s$, mEq/l								
Follicular	137.7 ± 0.5	139.4 ± 0.8	140.6 ± 0.9	141.2 ± 1.0	140.4 ± 0.8	137.1 ± 0.4	136.1 ± 0.5	136.3 ± 0.6
Luteal	136.9 ± 0.8	138.2 ± 0.7	139.4 ± 0.9	140.1 ± 1.2	139.7 ± 1.0	136.7 ± 0.7	135.9 ± 0.6	135.6 ± 0.5
OCP-A	136.1 ± 0.5	137.8 ± 0.6	139.5 ± 0.9	139.9 ± 0.8	138.9 ± 1.0	136.4 ± 0.3	136.3 ± 0.2	135.8 ± 0.4
$[K^+]_s$, mEq/l								
Follicular	3.76 ± 0.12	4.81 ± 0.09	4.89 ± 0.08	4.81 ± 0.13	4.16 ± 0.07	4.33 ± 0.06	4.21 ± 0.10	4.04 ± 0.08
Luteal	3.76 ± 0.07	4.92 ± 0.27	4.69 ± 0.07	4.74 ± 0.08	4.04 ± 0.01	4.25 ± 0.04	4.24 ± 0.08	4.13 ± 0.10
OCP-A	3.95 ± 0.09	4.77 ± 0.06	4.70 ± 0.09	4.74 ± 0.11	4.25 ± 0.06	4.38 ± 0.14	4.29 ± 0.09	4.11 ± 0.06

Table 4A. Responses of blood variables to 150 min dehydrating exercise and 180 min of *ad libitum* rehydration in the follicular and luteal phases and during administration of oral contraceptive pill A (OCP-A, n=6). Hematocrit (Hct), and hemoglobin (Hb), serum concentrations of sodium ($[Na^+]_s$) and potassium ($[K^+]_s$).

	Pre-exercise	Exercise			Rehydration			
	0 min	60 min	120 min	150 min	0 min	60 min	120 min	180 min
Hct , %								
Follicular	35.8 ± 1.0	37.1 ± 0.9	37.2 ± 1.0	37.6 ± 1.4	36.2 ± 1.1	35.6 ± 0.8	35.8 ± 0.8	35.2 ± 0.9
Luteal	38.4 ± 1.1	40.1 ± 1.2	40.5 ± 1.2	41.2 ± 1.5	39.3 ± 1.1	38.6 ± 1.0	38.9 ± 1.3	38.4 ± 1.1
OCP-B	36.7 ± 1.4	38.1 ± 1.4	38.4 ± 1.6	39.7 ± 1.5	37.5 ± 1.8	36.3 ± 1.6	36.4 ± 1.6	36.7 ± 1.3
Hb, g/dl								
Follicular	11.8 ± 0.5	12.4 ± 0.5	12.6 ± 0.5	12.8 ± 0.7	12.0 ± 0.5	11.7 ± 0.5	11.6 ± 0.6	11.5 ± 0.5
Luteal	12.9 ± 0.6	13.4 ± 0.6	13.5 ± 0.6	13.7 ± 0.7	12.9 ± 0.5	12.6 ± 0.6	12.7 ± 0.6	12.7 ± 0.6
OCP-B	12.30± 0.5	12.7 ± 0.5	13.0 ± 0.5	13.3 ± 0.6	12.3 ± 0.6	12.1 ± 0.5	12.1 ± 0.5	12.1 ± 0.5
$[Na^+]_s$, mEq/l								
Follicular	138.1 ± 0.4	140.2 ± 1.0	140.2 ± 0.5	142.0 ± 1.2	140.6 ± 0.6	137.8 ± 0.6	137.6 ± 0.5	137.3 ± 0.4
Luteal	136.6 ± 0.5	137.9 ± 0.6	139.3 ± 1.0	140.1 ± 1.5	139.0 ± 1.0	136.3 ± 0.8	136.1 ± 0.9	134.9 ± 0.7
OCP-B	136.6 ± 0.5	138.1 ± 0.8	139.8 ± 1.2	140.6 ± 1.5	139.8 ± 1.3	136.5 ± 0.7	136.5 ± 0.8	136.0 ± 0.6
$[K^+]_s$, mEq/l								
Follicular	3.84 ± 0.13	4.71 ± 0.14	4.78 ± 0.27	4.62 ± 0.19	4.09 ± 0.10	4.21 ± 0.07	4.09 ± 0.03	3.98 ± 0.04
Luteal	3.86 ± 0.09	4.92 ± 0.17	5.00 ± 0.18	4.97 ± 0.21	4.17 ± 0.08	4.43 ± 0.09	4.32 ± 0.06	4.10 ± 0.08
OCP-B	3.87 ± 0.11	4.91 ± 0.24	4.73 ± 0.10	4.70 ± 0.15	4.03 ± 0.07	4.12 ± 0.14	4.05 ± 0.08	3.90 ± 0.07

Table 4B. Responses of blood variables to 150 min dehydrating exercise and 180 min of *ad libitum* rehydration in the follicular and luteal phases and during administration of oral contraceptive pill B (OCP-B, n = 5). Hematocrit (Hct), and hemoglobin (Hb), serum concentrations of sodium ($[Na^+]_s$) and potassium ($[K^+]_s$).

	Pre-Exercise	End-exercise	Rehydration		
	0 min	150 min	0 min	120 min	180 min
PRA, ng ANG I·ml^{-1}·hr^{-1}					
Follicular	0.88 ± 0.25	5.04 ± 1.17	1.29 ± 0.24	1.12 ± 0.21	1.17 ± 0.29
Luteal	2.15 ± 0.51	7.92 ± 2.28	2.31 ± 0.48	2.31 ± 0.48	1.18 ± 0.46
OCP-A	1.29 ± 0.21	4.48 ± 0.79	2.50 ± 0.52	2.11 ± 0.53	2.09 ± 0.48
$[ALD]_p$, pg/ml					
Follicular	60.4 ± 21.8	268.1 ± 84.3	153.6 ± 31.2	97.4 ± 21.0	64.6 ±22.4
Luteal	169.2 ± 32.6	406.8 ± 95.8	228.9 ± 63.1	145.5 ± 27.7	145.5 ± 40.5
OCP-A	77.3 ± 17.8	259.0 ± 14.6	138.7 ± 9.1	110.8 ± 20.0	60.0 ± 19.5
$[ANP]_p$, pg/ml					
Follicular	47.3 ± 6.3	116.8 ± 17.7	66.9 ± 9.6	35.5 ± 5.1	31.8 ± 4.3
Luteal	41.9 ± 6.8	96.2 ± 13.8	61.0 ± 11.0	34.1 ± 5.4	34.6 ± 5.3
OCP-A	45.1 ± 5.3	106.7 ± 18.9	53.0 ± 5.7	38.5 ± 5.6	38.5 ± 5.9

Table 5A. Responses of plasma renin activity (PRA), and plasma concentrations of aldosterone ($[ALD]_p$) and atrial natriuretic peptide ($[ANP]_p$) to 150 min dehydrating exercise and 180 of *ad libitum* rehydration in the follicular and luteal phases, and during administration of oral contraceptive pill A (OCP-A, n=4).
Data are expressed as mean ± SEM.

	Pre-Exercise	End-exercise	Rehydration		
	0 min	150 min	0 min	120 min	180 min
PRA, ng ANG I·ml^{-1}·hr^{-1}					
Follicular	1.01 ± 0.28	3.69 ± 2.40	1.78 ± 0.77	1.06 ± 0.23	0.94 ± 0.27
Luteal	2.02 ± 0.37	5.88 ± 1.65	5.73 ± 1.35	3.55 ± 0.38	2.62 ± 2.30
OCP-B	0.86 ± 0.05	4.00 ± 2.11	2.36 ± 1.05	1.44 ± 0.35	2.88 ± 1.42
$[ALD]_p$, pg/ml					
Follicular	50.8 ± 9.4	159.5 ± 84.9	86.2 ± 49.6	45.6 ± 6.5	32.0 ± 5.4
Luteal	125.6 ± 13.8	534.4 ± 65.6	303.3 ± 42.7	183.0 ± 28.3	147.8 ± 27.5
OCP-B	74.6 ± 26.9	286.0 ± 81.9	147.2 ± 53.9	78.0 ± 19.8	64.0 ± 16.0
$[ANP]_p$, pg/ml					
Follicular	46.7 ± 9.9	110.8 ± 38.6	51.5 ± 9.3	37.1 ± 5.5	37.0 ± 5.1
Luteal	38.4 ± 7.5	71.0 ± 18.8	49.6 ± 13.3	27.2 ± 2.6	26.6 ± 3.7
OCP-B	40.1 ± 4.1	84.7 ± 17.2	39.0 ± 4.6	35.6 ± 1.9	36.4 ± 3.1

Table 5B. Responses of plasma renin activity (PRA), and plasma concentrations of aldosterone ($[ALD]_p$) and atrial natriuretic peptide ($[ANP]_p$) to 150 min dehydrating exercise and 180 of *ad libitum* rehydration in the follicular and luteal phases, and during administration of oral contraceptive pill B (OCP-B, n=4).
Data are expressed as mean ± SEM.

APPENDIX A
Figures 1-4

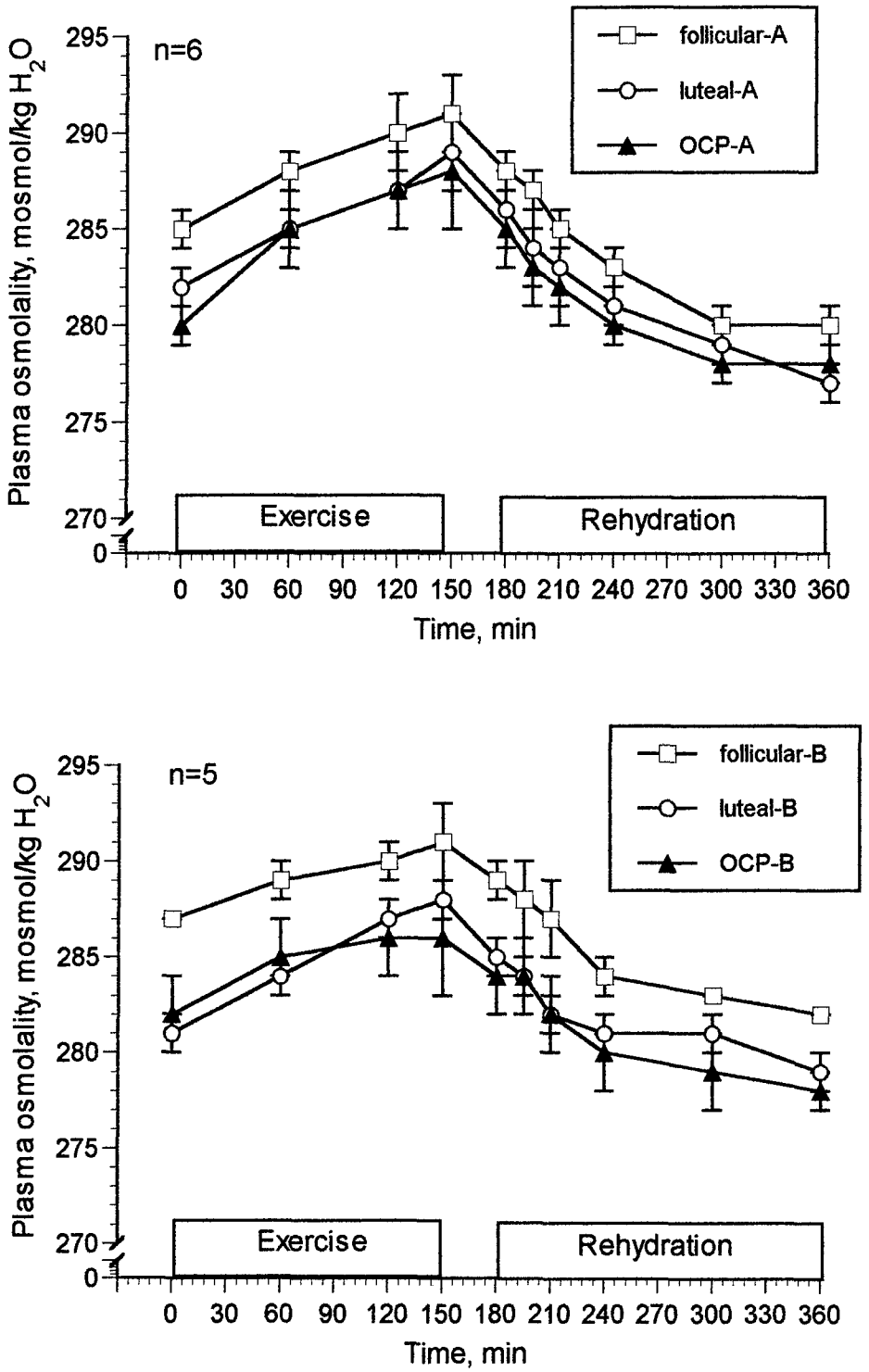

Figure 1. Plasma osmolality during dehydrating exercise and 180 min of *ad libitum* rehydration in the follicular and luteal phases, and with oral contraceptive (OCP) administration with pill A (*top*) and pill B (*bottom*). Data are expressed as mean ± SEM.

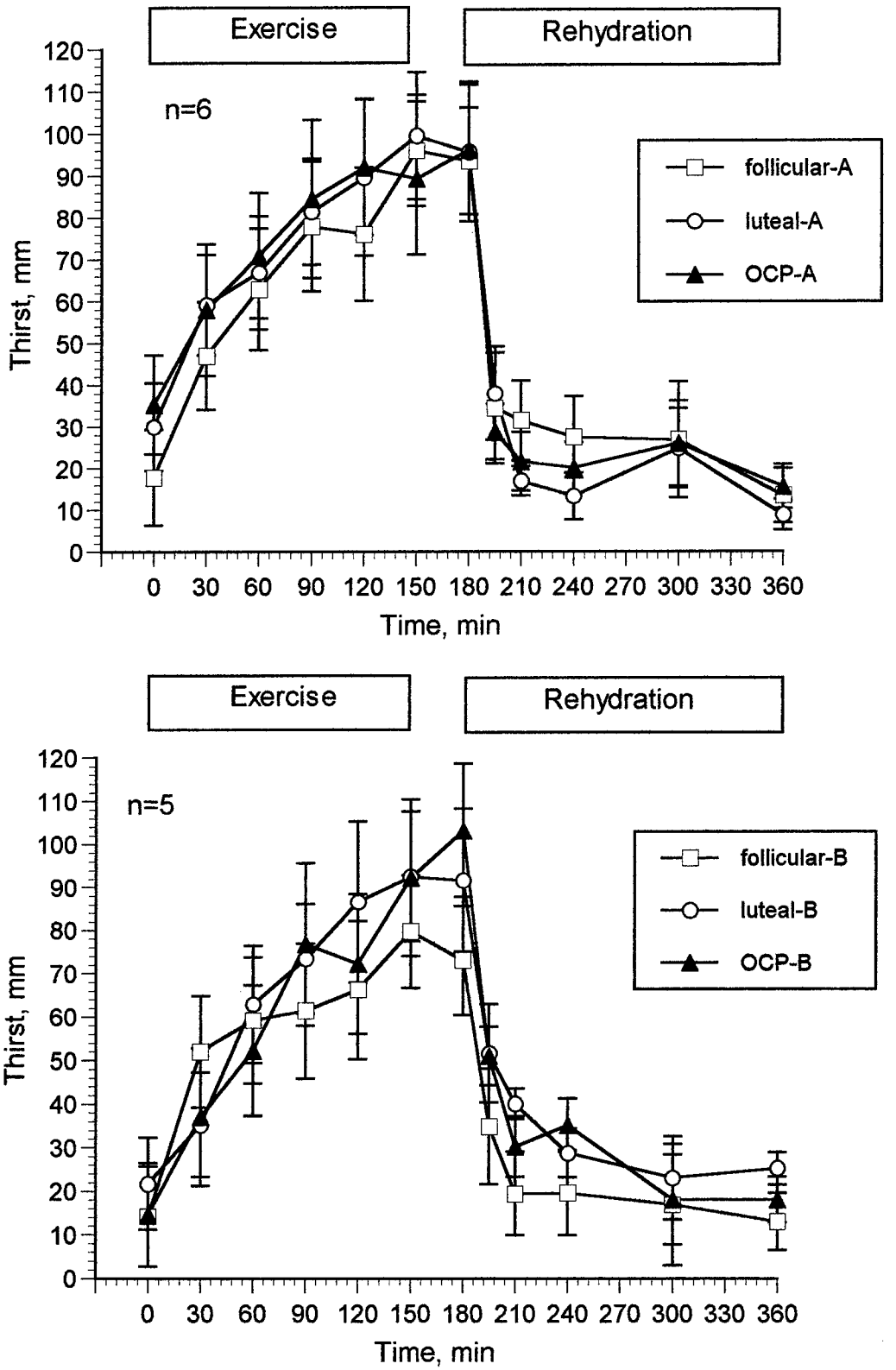

Figure 2. Perceptions of thirst ratings during dehydrating exercise and 180 min of *ad libitum* rehydration in the follicular and luteal phases, and with oral contraceptive (OCP) administration with pill A (*top*) and pill B (*bottom*). Data are expressed as mean ± SEM.

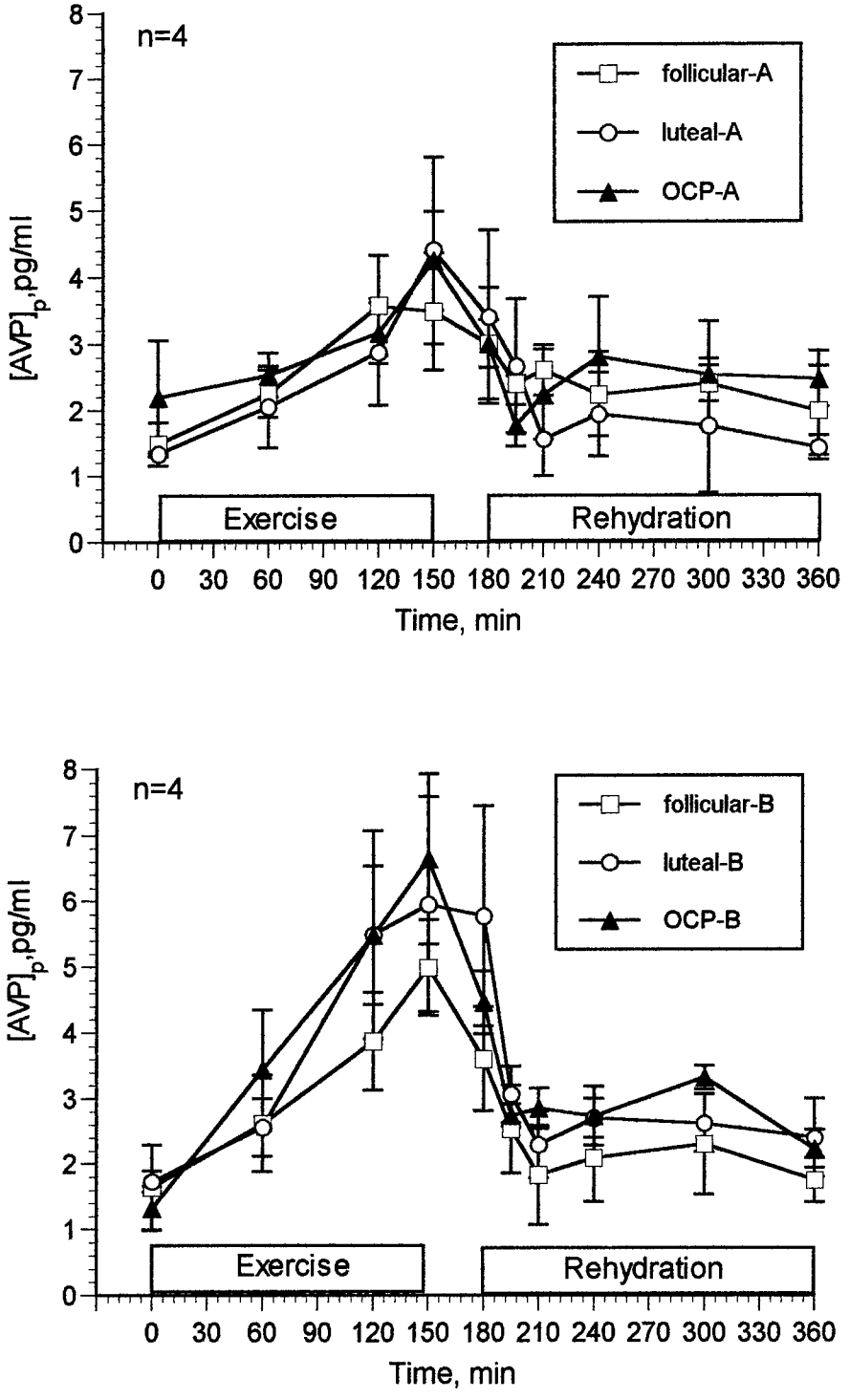

Figure 3. Plasma concentration of arginine vasopressin ($[AVP]_p$) during dehydrating exercise and 180 min of *ad libitum* rehydration in the follicular and luteal phases, and with oral contraceptive (OCP) administration with pill A (*top*) and pill B (*bottom*). Data are expressed as mean ± SEM.

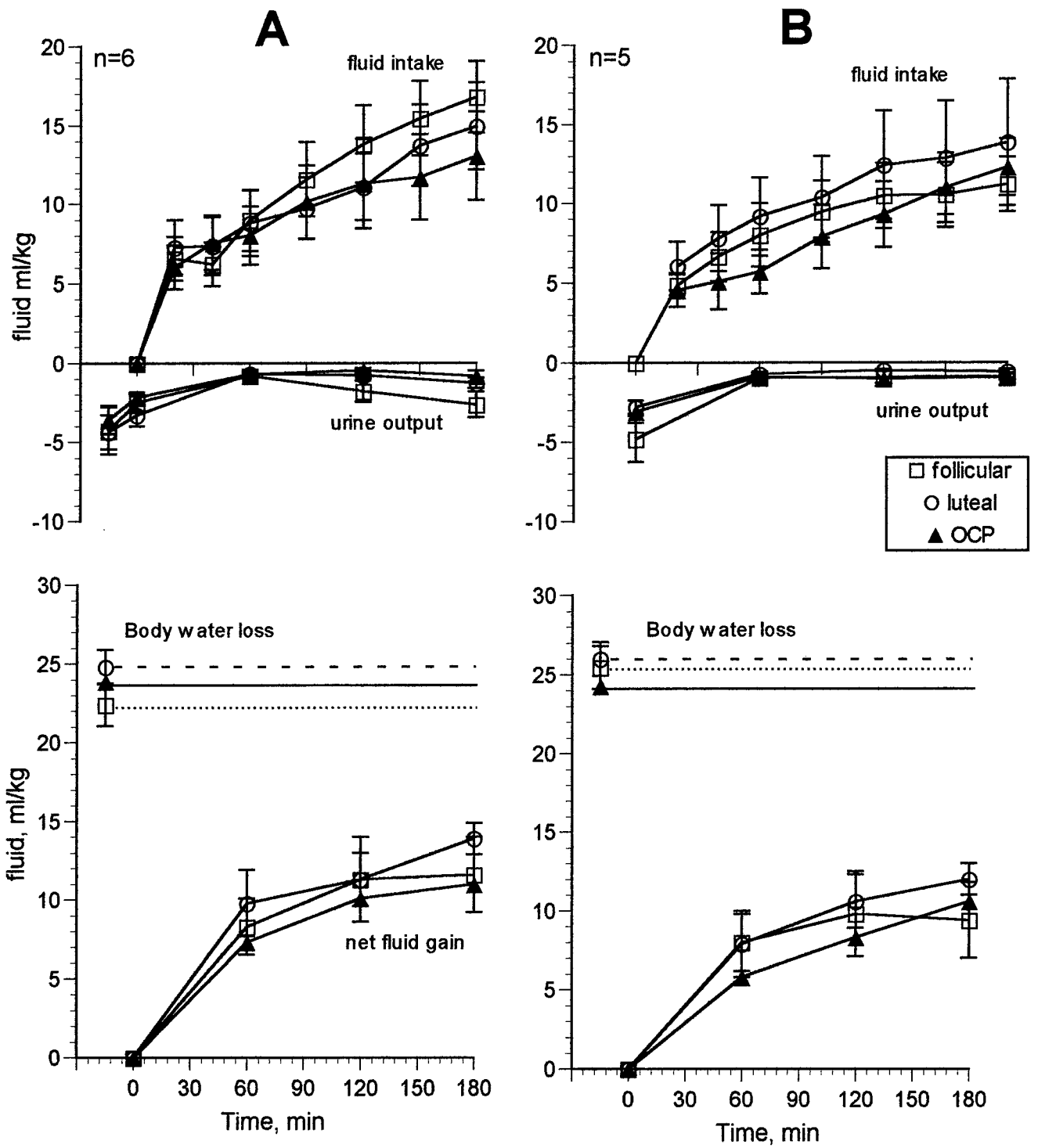

Figure 4. Fluid intake and urine output during rehydration (*top*) and changes in net fluid gain during *ad libitum* rehydration (*bottom*) in the control follicular and luteal phases, and with oral contraceptive (OCP) administration with pill A (*left*) and pill B (*right*). Total body water loss is difference from pre-dehydration levels. Data are expressed as mean ± SEM.

DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
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REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y) 28 July 03

MEMORANDUM FOR Administrator, Defense Technical Information Center (DTIC-OCA), 8725 John J. Kingman Road, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for this Command. Request the limited distribution statement for the enclosed accession numbers be changed to "Approved for public release; distribution unlimited." These reports should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Kristin Morrow at DSN 343-7327 or by e-mail at Kristin.Morrow@det.amedd.army.mil.

FOR THE COMMANDER:

Encl

PHYLIS M. RINEHART
Deputy Chief of Staff for
Information Management

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